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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,645	11/13/2001	Menzo Jans Emco Havenga	5006.1US	4875

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,645	HAVENGA ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/30/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This office action is in response to an amendment filed 9/30/03. Claims 1-27 and 29-47 have been cancelled. Claims 28 and 48 are pending. An IDS filed 9/30/03 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action. There is a new ground of rejection herein and therefore, this rejection is Non-Final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a method for delivering a nucleic acid of interest in which a critical element is a recombinant adenovirus (rAd).fiber proteins comprised of at least one protein fragment of an adenovirus serotype C and at least a knob domain of a fiber protein of a second ad serotype. The recombinant adenovirus has the functional limitation of tropism for mesenchymal stem cells.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical

and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus. In the instant invention, applicants recite a large genus of fibers comprised of at least one protein fragment of a subgroup C adenovirus and at least a knob domain from a second ad serotype. In the instant specification, applicants teach construction of a rAd using constructs such as pBr/Ad.BamRΔFib that have been deleted of ad5 fiber sequences (see e.g. paragraph 0091). These constructs are inserted with fiber sequences from a second adenovirus serotype such as 16, 35, 40-S and 51. There is no actual reduction to practice or clear depiction of what structures or properties of the Ad5 protein fragments are required for generation of the recited recombinant adenovirus fiber proteins for tissue tropism for mesenchymal stem cells. Neither applicant nor the prior art provide a correlation between the structure of any protein fragment and their tropism. In an unpredictable art, the disclosure of no species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus. Given the diversity of protein fragments of an adenovirus serotype of subgroup C and the lack of written disclosure of the structural characteristics, and the lack of written disclosure of the functional characteristics required of the fragment for tropism for mesenchymal cells, it is concluded that applicant was not in possession of their invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The invention recites a method for delivering a nucleic acid of interest to mesenchymal stem cells (MSC) using a rAd with a fiber comprised of at least one protein fragment of an adenovirus C serotype and at least a knob domain from a serotype selected from the group consisting of serotype 16, 32, 35, 40-S and 51. This invention requires a complex combination of molecular cloning in combination with viral and cell culture techniques to generate the recombinant adenovirus in combination with clinical techniques form administration of the particles to subjects.

2) Scope of the invention. The invention recites administration of the recombinant adenovirus to mesenchymal stem cells to deliver a nucleic acid of interest. The only recited uses are for gene therapy.

3) Number of working examples and guidance. The instant specification teaches means of constructing and purifying rAd comprised of chimeric coat proteins. Furthermore, the specification teaches transduction of human mesenchymal stem cells in culture. Applicants teach on page 2, paragraph 0003 that the invention is designed for gene therapy and some prospective applications are described on page 9, paragraph 0035-0037. However, the specification fails to demonstrate any examples or guidance for deliverance of nucleic acids to cells *in vivo*.

4) State of the art. There has been much interest in the development of viruses that transduce therapeutic genes into target tissues. However, the lack of established protocols and positive results has hampered the use of such inventions. Therefore, the art must be considered to be poorly developed.

5) Unpredictability of the art. Adenoviral vector use for gene therapy is hindered by the transient nature of the transgene expression coupled with host immune responses. Approaches to prolong transgene expression by multiple injections of adenovirus or to increase transgene expression cause have proven futile in the face of these host immune responses to the recombinant adenoviral vector (Kmiec, American Scientist p 243 and Anderson, Nature p. 28). Use of adenovirus is thwarted by the humoral immune responses as taught by Verma and Somia Nature p. 241; "Unfortunately for gene therapy, most of the human population will probably have antibodies to adenovirus from previous infection with the naturally occurring virus" (Verma and Somia, p 241). And "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less desirable on a practical scale because the immune

response helps to eliminate the vector and to decrease the expression of the transduced gene (p. 4, column 2).

The unpredictability of use of the instantly claimed invention in humans is accentuated by the lack of methods or processes disclosed in the specification. Many parameters must be addressed for *in vivo* use such as tumor cell selectivity in humans, lack of toxicity to normal tissues, and the effect of the antiviral immune response as well as doses to be administered, dose schedules etc. For example, what level of expression is necessary to achieve therapeutic affects without toxicity to normal cells that results from leaky expression of the viral gene required for replication? The method of delivery presents an obstacle for adenovirus use. "While reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle positioned in a tumour deposit. This strategy achieves a relatively low efficiency of gene delivery, which is confined to tumour cells immediately adjacent to the needle track. Plasmids or viral particles delivered in this way do not permeate freely through the interstitial fluid bathing the tumour." (Russell, European Journal of Cancer p 1165, column 2).

6) Amount of Experimentation Required. The invention recites use of a rAd particle for deliverance of a nucleic acid of interest to MSC. In view of the unpredictability of the art of therapeutic gene expression in mammalian subjects, the lack of established clinical protocols and the inability to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. The level of skill in the art covering this invention was high at the time of invention; however, given the unpredictability of the art, the poorly developed state of the art, the lack of working examples and the lack of guidance

provided by applicants, the skilled artisan would have to have conducted undue experimentation to practice the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3291.

Maria B Marvich, PhD
Examiner
Art Unit 1636

December 17, 2003

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600